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Brief Clinical Report

Limb-Pelvis Hypoplasia/Aplasia: A Discrete Entity in the Fibuloulnar Developmental Field Complex

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The limb-pelvis hypoplasia/aplasia (LPHA) syndrome is a rare condition of skeletal malformations affecting the ulnae, pelvic bones, fibulae and femora, sometimes associated with extraskeletal defects. Most reported patients are from the Middle East, and autosomal recessive inheritance was clearly demonstrated on the basis of multiple occurrences of affected sibs born to consanguineous matings. Here we report on a baby girl presenting with the phenotypic characterics of LPHA. This is second observation of LPHA from Italy, and the fourth outside the Middle East. A paternal first cousin once removed had unilateral fibular hypoplasia and absence of the the 4th and 5th digital rays. The possible link between these cases is discussed in the light of the developmental field theory. Am. J. Med. Genet. 68:190–194, 1997

KEY WORDS: femoral a/hypoplasia; fibular a/hypoplasia; FFU complex; proximal focal femoral deficiency; autosomal recessive

INTRODUCTION

The limb-pelvis hypoplasia/aplasia (LPHA) syndrome is an autosomal recessive condition comprising severe malformations of lower and upper limbs and extraskeletal anomalies [Al-Awadi et al., 1985; Raas-Rothschild et al., 1988; Camera et al., 1993]. Although the phenotype is variable, all patients described so far have defects of the fibuloulnar developmental field. The boundaries of this field were delineated based on clinical and experimental criteria [Lewin and Opitz, 1986]. In typically affected cases, the ulnae, proximal portions of the femora, fibulae, postaxial digital rays, pelvic bones and patellae are involved to variable degree. Additional anomalies, affecting other limb bones and pelvic bones may appear in the most severe cases.

We report on a girl who presented with a combination of skeletal and extraskeletal anomalies suggestive of the LPHA syndrome. A first cousin once removed had a unilateral fibular defect.

CLINICAL REPORT

The patient is the first child of healthy, nonconsanguineous parents. She was born to a 26-year-old mother and a 27-year-old father. The pregnancy was complicated by nephrolithiasis and urinary infections, for which the mother was treated with cephalosporins during the first trimester. Pelvic and femoral abnormalities were noted at 7 months of gestation by ultrasound examination. Birth was at the 42nd week by normal vaginal delivery with a weight of 1,870 g, length of 32.5 cm, and occipitofrontal circumference (OFC) of 31.8 cm (2nd centile). Apgar scores were 9 and 7 at 1 and 5 minutes, respectively. Gross malformations of the lower limbs were immediately evident.

Physical examination showed broad nasal bridge with wide-set eyes, bulbous nose, anteverted nares, long philtrum, pointed chin, short neck, barrel-shaped chest with mild pectus excavatum, diastasis recti, preaxial polydactyly of the right hand with presence of a soft tissue nubbin, upwardly displaced genitalia, and a pilonidal dimple. The lower limbs were markedly hypoplastic and bent, and the feet were grossly misplaced, the right foot presenting with an anterior sole (Fig. 1). The clinical course was characterized by episodes of respiratory insufficiency with laryngeal stridor, most commonly during or immediately after meals. The girl died at 2 months due to cardiorespiratory insufficiency.

Roentgenological investigations demonstrated bilateral femoral and fibular aplasia, with hypoplastic pelvis, particularly affecting the iliac bones, which appeared vertical (Fig. 2). Upper limb bones were normal. A horseshoe kidney and vescico-ureteral reflux were detected upon urography. Ultrasound study showed a patent foramen ovale. Chromosomes were normal (46,XX). No additional malformations were noted at autopsy.

Family history showed that a paternal male first cousin once removed (Fig. 3) had a malformation of the

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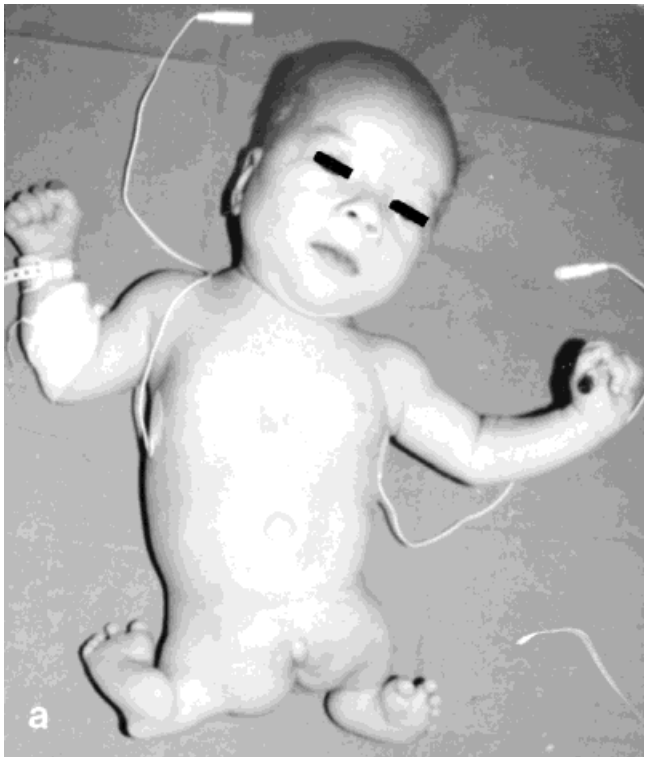

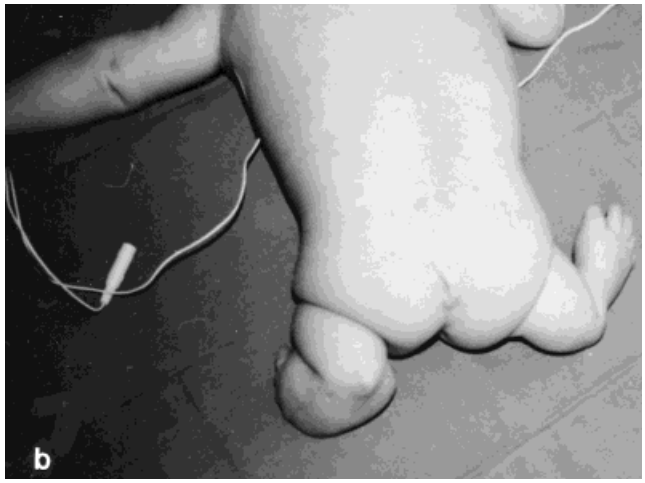

Fig. 1. The proposita. **a**: Anterior view; the necrotic area corresponding to the removed extra digit is visible as a black spot next to the left thumb. **b**: Dorsal view illustrating the pilonidal dimple.

left leg and foot. Roentgenograms (Fig. 4) showed a markedly hypoplastic fibula, with presence of a small ovoid bone corresponding to its distal portion, a short and bowed tibia, fused astragalus and calcaneus, absence of the 4th and 5th digital rays, and hypoplasia of the 2nd and 3rd digital rays. The 2nd and 3rd rays had only two phalanges, and the 3rd metatarsal was proximally elongated and fused with the tarsal bones.

Fig. 2. Roentgenogram of the proposita's lower limbs.

DISCUSSION

The presence of a distinct familial condition characterized by hypo/aplasia of the pelvic bones and of the limbs, mainly affecting ulnae, fibulae, and femora, is documented by several independent reports of affected sibs [Al-Awadi et al., 1985; Raas-Rothschild et al., 1988; Schinzel, 1990; Camera et al., 1993]. Autosomal recessive inheritance was inferred based on parental consanguineity in three families [Al-Awadi et al., 1985; Raas-Rothschild et al., 1988; Farag et al., 1993]. This is the second report of an Italian patient presenting with this phenotype and, to our knowledge, the fourth report from outside the Middle East, the other cases having been observed in families of Brazilian [Richieri-Costa, 1987] and mixed Swiss-Hungarian [Schinzel, 1990] origin, respectively.

The phenotype of this condition is variable. Skeletal abnormalities include ulnar hypo/aplasia, oligodactyly, pelvic hypoplasia, which can affect all pelvic bones, femoral a/hypoplasia, and fibular a/hypoplasia, with defects of the fibular rays. Less commonly, tibial a/hypoplasia has been described, in one instance combined with femoral bifurcation [Farag et al., 1993]. The radii may appear slightly short and/or misplaced with radioulnar synostosis. Additional anomalies affecting extraskeletal structures have been reported. These include renal agenesis, occipital meningocele, hypoplastic cerebellum, pilonidal cyst or dimple, diaphragmatic hernia, common mesentery, and agenesis of the gallbladder, uterus and vagina.

The phenotypes described by Fuhrmann et al. [1980] and by Al-Awadi et al. [1985] have been considered different conditions based essentially on the presence of

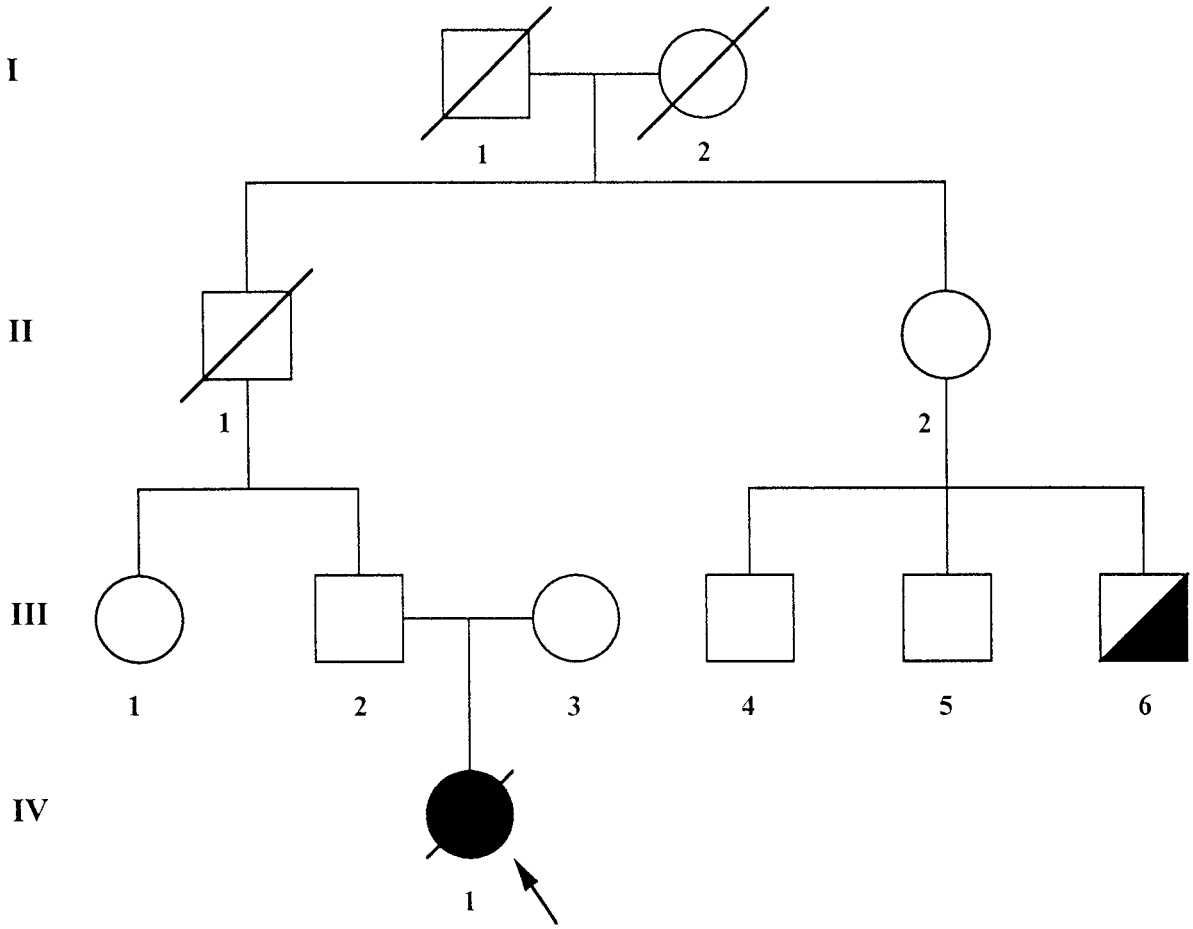

Fig. 3. Pedigree of the family. ● : LPHA; ◪ :Unilateral fibular hypoplasia.

normal upper limbs, except for postaxial polydactyly, and of markedly bowed, boomerang-like femora in the former, whereas the latter showed tetramelic limb defects. However, the recently described cases of Kumar et al. [1997] combined ulno-fibular defects, postaxial polydactyly of feet and bowed femora, suggesting that the two conditions might represent variable expressions of the same defect affecting the fibuloulnar developmental field. This condition was named LPHA syndrome by Raas-Rotshchild et al. [1988], and the pedigree studied by Kumar et al. [1997] provides further confirmation of autosomal recessive inheritance, since it contains four cases born to three different consanguineous matings.

The case reported here differs from those described by Fuhrmann et al. [1980] for the absence, rather than bowing, of femora, and for the type of hand polydactyly, which was preaxial and unilateral, while Fuhrmann et al.'s [1980] cases displayed symmetric postaxial polydactyly. Differences between our case and other patients affected with the LPHA syndrome [Al-Awadi et al., 1985; Richieri-Costa, 1987; Raas-Rothschild et al., 1988; Schinzel et al., 1990; Camera et al., 1993; Farag et al., 1993] are mainly related to ulnar involvement in typical LPHA cases and, again, to the presence of preaxial polydactyly. In addition, the girl described here did not have the characteristic nail hypoplasia/aplasia commonly found in the LPHA syndrome. Despite these differences, the distribution of skeletal malformations mainly along the territory encompassed by the fibuloulnar developmental field suggests that our proposita has the LPHA syndrome.

The pattern of anomalies found in the LPHA syndrome is similar to that observed in the femur-fibula-ulna (FFU) complex, which is the most common fibuloulnar dysostosis. However, the FFU complex is usually sporadic and limb involvement is often asymmetrical and unilateral [Lenz et al., 1993]. The malformations observed in LPHA syndrome are also more extensive compared to FFU dysostosis, although peromelia and amelia are considered as the most severe end of the FFU spectrum [Lenz et al., 1993]. The cause of the FFU dysostosis is currently unknown. In view of the similarities between the FFU complex and the skeletal manifestations in focal dermal hypoplasia, Lenz et al. [1993] proposed that the former could originate from localized somatic mutations occurring during development. Lewin and Opitz [1986] also suggested

Fig. 4. Roentgenograms of the distal portion of the left leg and of the left foot of the proposita's first cousin once removed. The fibula is visible as a small ovoid bone in **a**, and presence of 3 hypoplastic digital rays is shown in **b**.

that "FFU dysostosis could be a sublethal defect allowing for survival in mild cases but being lethal in severe cases." This interpretation, which was based on a report of two affected sibs, a girl with monomelic anomalies, and a male fetus with tetramelic defects [Zlotogora et al., 1983], is compatible with the somatic mutation hypothesis. Limb anomalies in the male fetus [Zlotogora et al., 1983], who died during the 14th week of pregnancy, were similar to those found in the LPHA syndrome. More recently, Lenz et al. [1993] described another sib pair affected with FFU dysostosis, a boy with symmetrical involvement of the legs, and a girl with unilateral ulnar aplasia.

Thus, it seems that there is at least one form of fibuloulnar developmental defect, transmitted in an autosomal recessive fashion and distinct from the FFU complex, which is characterized by more severe malformations, with frequent involvement of extraskeletal structures, such as kidneys, Mullerian derivatives, and the brain. Affected patients may present with tibial defects, just like more severe cases of FFU dysostosis. Rarely, the radial side may be mildly affected, as in the present patient. Although the sib pairs reported by Zlotogora et al. [1983] and by Lenz et al. [1993] should be kept distinct purely on clinical criteria, they might represent the mild end of the LPHA spectrum. Eventually, the nosological issue of lumping and splitting will be solved once molecular dissection of the phenotypes will be achieved. Also, in view of the relatively frequent occurrence of renal anomalies, the LPHA syndrome could be considered as an example of acrorenal polytopic field defect [Dieker and Opitz, 1969].

The recurrence of fibular defects in a distant relative is unusual. The simplest explanation is, of course, pure coincidence. However, recurrence of fibular defects has been observed by some authors. For instance, Hamanishi [1980] reported on two sets of first cousins presenting with proximal focal femoral deficiency (PFFD), which is synonymous with the FFU spectrum. More re-

cently, Sorge et al. [1995] reported on a father and son affected with variable manifestations of PFFD/FFU. These observations raise the possibility of an autosomal dominant form of FFU dysostosis characterized by reduced penetrance and variable expressivity. Finally, taking into account the Lenz et al. [1993] hypothesis of somatic mosaicism, the affected relative of our proposita could have been a heterozygous carrier of the mutation, and his leg anomaly be caused by reduction to homozygosity in the leg primordium during embryonic development.

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REFERENCES

Al-Awadi SA, Teebi AS, Farag TI, Naguib KM, El-Khalifa MY (1985): Profound limb deficiency, thoracic dystrophy, unusual facies, and normal intelligence: A new syndrome. J Med Genet 22:36–38.

Camera G, Ferraiolo G, Leo D, Spaziale A, Pozzolo S (1993): Limb/pelvis-hypoplasia/aplasia syndrome (Al-Awadi/Raas-Rothschild syndrome): Report of two Italian sibs and further confirmation of autosomal recessive inheritance. J Med Genet 30:65–69.

Dieker H, Opitz JM (1969): Studies of malformation syndromes XVI: Association of acral and renal malformations. New York: Alan R Liss, Inc, for the National Foundation-March of Dimes, BD:OAS V (3):68–77.

Farag TI, Al-Awadi SA, Marafie MJ, Bastaki L, Al-Othman SA, Mohammed FM, AlSuliman IS, Murthy DSK (1993): The newly recognized limb/pelvis-hypoplasia/aplasia syndrome: Report of a Bedouin patient and review. J Med Genet 30:62–64.

Fuhrmann W, Fuhrmann-Rieger A, de Sousa F (1980): Poly-, syn- and oligodactyly, aplasia or hypoplasia of fibula, hypoplasia of pelvis and bowing of femora in three sibs—a new autosomal recessive syndrome. Eur J Pediatr 133:123–129.

Hamanishi C (1980): Congenital short femur. Clinical, genetic and epidemiological comparison of the naturally occurring condition with that caused by thalidomide. J Bone Joint Surg 62B:307–320.

Kumar D, Mueller RF, Duggan MB, Brocklebank T (1997): Familial aplasia/hypoplasia of pelvis, femur, fibula and ulna with abnormal digits in an inbred Pakistani muslim family: An example of autosomal recessive disorder with overlapping features of the syndromes of Fuhrmann, Al-Awadi, and Raas-Rothschild. Am J Med Genet (in press).

Lenz W, Zygulska M, Horst J (1993): FFU complex: An analysis of 491 cases. Hum Genet 91:347–356.

Lewin SO, Opitz JM (1986): Fibuar a/hypoplasia: Review and documentation of the fibular developmental field. Am J Med Genet (Suppl 2):215–238.

Raas-Rothschild A, Goodman RM, Meyer S, Bat-Miriam, Katznelson M, Winter ST, Gross E, Tamrkin M, Ben-Ami T, Nebel L, Mashiachi S (1988): Pathological features and prenatal diagnosis in the newly recognized limb/pelvis hypoplasia/aplasia syndrome. J Med Genet 25:687–697.

Richieri-Costa A (1987): Profound limb deficiency, thoracic anomalies, unusual facies and normal intelligence—the Al-Awadi syndrome—report of a Brazilian patient. Rev Brasil Genet 10:611–616.

Schinzel A (1990): Phocomelia and additional anomalies in two sisters. Hum Genet 84:539–541.

Sorge G, Ardito S, Genuardi M, Pavone V, Rizzo R, Conti G, Neri G, Katz BE, Opitz JM (1995): Proximal femoral focal deficiency (PFFD) and fibular a/hypoplasia (FA/H): A model of a developmental field defect. Am J Med Genet 55:427–432.

Zlotogora J, Rosenmann E, Menashe M, Robin GC, Cohen T (1983): The femur, fibula, ulna (FFU) complex in siblings. Clin Genet 24:449–452.